REMARKS

These remarks are in response to the Office Action mailed March 27, 2003. Claims 7-11 have been canceled without prejudice to Applicants' right to prosecute the subject matter in any divisional, continuation, continuation-in-part, or other application. Claims 1, 2, 6, 15, and 18 have been amended. Support for the amendments can be found throughout the specification as filed. Certain amendments were made to remove subject matter that was directed to a non-elected invention. New claims 20 and 21 have been added. Support for the new claims can be found, for example, in Figure 11 and on page 21, lines 26-28. No new matter is believed to have been introduced.

I. OBJECTION TO CERTAIN CLAIMS

The Office Action alleges that claims 1, 13, 15, and 18 are objected to as having portions of the claim drawn to a non-elected invention. Claims 13 and 18 have been restricted to DNA molecules and/or sequences, however it is not clear to Applicants what parts of claim 1 and 15 are drawn to non-elected inventions. Claim 2 is objected to for the use of the language "derived". Claim 18 is objected to because there is no items (a-d) preceding items (e-i) of claim 18. Applicants believe that the foregoing amendments overcome these objections. Accordingly, Applicants respectfully request withdrawal of the foregoing amendments.

II. REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-2, 6, 13(c), and 15-16 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action indicates that the use of the phrase "dominant negative effect" is allegedly indefinite. Applicants respectfully traverse this rejection.

Dominant negative mutants refer to proteins that "function by overwhelming the wild type protein and preventing it from functioning" (*Genes VII* by Benjamin Lewis, Oxford University Press (2000), p. 282 and 901; see Appendix 1 attached hereto).

One example of a fragment of the $TAF_{II}105$ polypeptide described in the specification, which has a dominant negative effect, is $TAF_{II}105\Delta C$. The reason that $TAF_{II}105\Delta C$ acts as a dominant negative mutant is that it produces an inactive protein which is not only unable to assemble into the $TF_{II}D$ complex, but is able to bind the p65/Re1A NF-κB subunit and to compete with the endogenous $TAF_{II}105$ for binding to the p65/Re1A NF-κB subunit. In this way, $TAF_{II}105\Delta C$ neutralizes the function of the wild type protein (See Silkov et al., J. Biol. Chem., 277:17821-17829, 2002; Appendix 2 attached hereto).

The term "dominant negative mutant" has been accepted by the reviewers of all the articles published by the inventors using this mutant, as listed below and attached hereto as Appendices 2-6).

- Yamit-Hezi, A. and Dikstein, R. (1998). $TAF_{II}105$ Mediates Activation of Anti-Apoptotic Genes by NF-kB. EMBO J. 17, 5161-5169 (Appendix 3).
- Wolstein, O., Silkov, A., Revach, M. and Dikstein, R. (2000). Specific Interaction of $TAF_{II}105$ with OCA-B is involved in Activation of Octamer-Dependent Transcription. J. Biol. Chem. 275, 16459-16465 (Appendix 4).
- Yamit-Hezi, A., Nir, S., Wolstein, O. and Dikstein, R. (2000). Interaction of $TAF_{II}105$ with Selected p65/RelA Dimers is Associated with Activation of Subset of NF-kB Genes. J. Biol. Chem. 275, 18180-18187 (Appendix 5).
- Matza, D., Wolstein, O., Dikstein, R., and Shachar, I. (2001). Invariant Chain Induces B Cell Maturation by Activating $TAF_{II}105$ -NF-kB Transcription Program. J Biol. Chem. 276, 27203-27206 (Appendix 6).
- Silkov, A. Wolstein, O., Shachar, I and Dikstein, R. (2002). Enhanced apoptosis of B and T lymphocytes in $TAF_{II}105$ Dominant Negative Transgenic Mice is Linked to NF-kB. J. Biol. Chem. 277, 17281-17829 (Appendix 2).

Applicants submit that the term "dominant negative mutant" is well understood in the art and thus clearly sets forth the metes and bounds of the invention. Accordingly, Applicants respectfully request withdrawal of the §112, second paragraph rejection.

III. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-2, 6, 13(c), and 15-16 stand rejected under 35 U.S.C. §112, first paragraph, because while the specification is enabled for a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, where said fragment decreases the basal activity of NF-κB, allegedly does not provide enablement for a DNA sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, wherein said fragment has a dominant negative effect on the "normal biological activity" of the $TAF_{II}105$ polypeptide. Applicants respectfully traverse this rejection.

The Examiner is respectfully directed to the attached 37 C.F.R. §1.132 Declaration of inventor, Dr. Dikstein, (the "Declaration") attached hereto as Annex A. In the Declaration, Dr. Dikstein indicates that experiments presented in the application together with the experiments of exogenously expressed $TAF_{II}105$ proteins, wild type, and mutants, and the respective biochemical data, provide further evidence (in addition to that in the application) showing proof of principle that the fragment has a dominant negative effect on NF-κB (see, e.g., Appendix 3; Yamit-Hezi, A. and Dikstein, R., "$TAF_{II}105$ Mediates Activation of Anti-Apoptotic Genes by NF-kB." EMBO J. 17:5161-5169, 1998).

In addition, the Office Action mentions several times that the polypeptides increase or decrease the basal activity of NF-κB. The Examiner is respectfully directed to the Declaration wherein Dr. Dikstein points out that the results presented in the application relate to the induced activity of NF-κB, and not the basal activity (see, e.g., Figure 5a to 5d, and Figure 6c of the application). Dr. Dikstein also explains in the Declaration that p65 is a subunit of the NF-κB transcription factor and thus it represents NF-κB. The anti-apoptotic activity of NF-κB is conferred by p65 (see, e.g., Van Antwerp et al., 1996 (Appendix 7); and Beg and Baltimore, 1996 (Appendix 8)).

Applicants respectfully submit that the specification and claims are clearly enabled by the specification and further supported by the Declaration and attached references, which are provided to demonstrate further proof of principle for that which is disclosed in the specification as filed. The claimed invention is readily placed in the hands of the skilled person in the art without undue experimentation. Accordingly, Applicants respectfully request withdrawal of the §112, first paragraph rejection.

Claims 13, 15-16, and 18-19 stand rejected under 35 U.S.C. §112, first paragraph, because while the specification is enabled for a cDNA sequence encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2, or SEQ ID NO:1 or a fragment thereof, wherein the fragment comprises a nucleotide sequence encoding a fragment of the $TAF_{II}105$ polypeptide of SEQ ID NO:2, and where the fragment decreases the basal activity of NF-κB, allegedly does not provide enablement for a "pharmaceutical composition for inducing an apoptotic process in pathological cells, or the treating inflammation." The Office Action goes on to allege that, ". . . one cannot extrapolate the teaching of the specification to the scope of the claims because there is no correlation between *in vitro* induction of apoptosis by $TAF_{II}105\Delta C$ in transfected cells and *in vivo* treatment of cancer. . . ." On pages 9-15 of the Office Action the Applicants interpret the Action as suggesting that one cannot extrapolate the teaching of the specification to the scope of the claims, and that there is no correlation between the *in vitro* induction of apoptosis described in the specification and the claimed *in vivo* treatment of cancer. Applicants respectfully traverse this rejection.

It appears the Examiner is questioning the therapeutic/pharmaceutical aspects or benefit of the claimed invention. Considerations regarding the therapeutic benefit or pharmaceutical aspect are different from those made by the PTO in determining whether a claim is enabled. See, *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].")

Without patent protection, Applicants' opportunity to pursue the expensive research necessary to take the next step may be curtailed. The PTO stands as gatekeeper for technology. Applicants ask that the PTO make a careful, objective assessment of the issues it is competent to decide in exercising its gatekeeper authority. Surely the PTO is competent to decide whether an applicant has provided some objective data to support a claim. This determination should be a threshold one, however, and not an ultimate answer to the question of whether the proposed invention is "safe and efficacious". Those judgments are reserved by statute for the U.S. Food and Drug Administration.

The issue of "correlation" (i.e., between *in vitro* and *in vivo* activity) is related to the issue of the presence or absence of working examples. Correlation as described in the training

materials provided by the USPTO refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" because that example "correlates" with a disclosed or claimed method invention.

The issue of "correlation" is also dependent on the state of the prior art. Because the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating. See, Training Materials for Examining Patent Applications with Respect to 35 U.S.C. §112, first paragraph -- Enablement Chemical/Biotechnical Applications (see also, *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support in vivo applications)). The examiner is also reminded that a rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art. Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications.

The examiner must weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant in deciding whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, first paragraph -- Enablement Chemical/Biotechnical Applications. The determination should always be based on the weight of all the evidence.

For treating cancer, the goal is to achieve death of the cancerous cell. It does not matter if such a treatment involves an unnatural concentration of a compound that can promote apoptosis, such as $TAF_{II}105\Delta C$. The idea is to shift the balance between survival and death more towards

death (apoptosis). Dr. Dikstein provides in the Declaration that the cells used in the experiments described in the application (293 and HeLa cell lines) are standard, internationally recognized models for developing *in vivo* cancer treatments.

Again, the Examiner is respectfully directed to the Declaration (see, e.g., paragraphs 8-12, specifically). Dr. Dikstein recently published a study in which the effect of $TAF_{II}105\Delta C$ in a transgenic mice model system *in vivo*, and obtained results consistent with those *in vitro*, namely that this protein (at very low concentrations) inhibits transcription activation of NF-κB dependent anti-apoptotic genes (Silkov, A. Wolstein, O., Shachar, I and Dikstein, R. 2002. Enhanced apoptosis of B and T lymphocytes in $TAF_{II}105$ Dominant Negative Transgenic Mice is Linked to NF-kB. J. Biol. Chem. 277, 17281-17829 (Appendix 2)). Another example of an *in vitro* study that is confirmed *in vivo* can be found as follows: The involvement of NF-κB in anti-apoptotic gene activation in response the TNF cytokine is shown *in vitro* (Van Antwerp, D.J., Martin, S.J., Kafri, T., Green, D.R. and Verma I.M. 1996; Suppression of TNF-alpha-induced apoptosis by NF-κB. Science 274: 787-789 (Appendix 7)), and is confirmed *in vitro* and *in vivo* in the article: Beg, A.A. and Baltimore, D. 1996. An essential role for NF-κB in preventing TNF-α-induced cell death. Science 274: 782-784 (Appendix 8).

Applicants submit that based upon the evidence before the Examiner including (a) the *in vitro* studies using the 293 and HeLa cell lines in the application that are well recognized for their correlation to developing cancer treatments, and (b) evidence provided by Dr. Dikstein in her Declaration that shows further proof of principle in *in vivo* animal studies that the methods of the invention inhibit transcription activation of NF-κB dependent anti-apoptotic genes, the claims are fully supported and enabled by the specification and the knowledge of one of skill in the art. Accordingly, Applicants respectfully request withdrawal of the §112, first paragraph rejection.

Claims 12, and 13(d) stand rejected under 35 U.S.C. §112, first paragraph because the specification, while being enabling for an antisense of SEQ ID NO:1, which is capable of inhibiting its expression *in vitro*, allegedly does not reasonably provide enablement for an antisense of SEQ ID NO:1, which is capable of inhibiting its expression *in vivo* or a pharmaceutical composition for inducing an apoptotic process in pathological cells Applicants respectfully traverse this rejection.

The Examiner admits that the specification is enabling for the antisense sequence inhibiting expression *in vitro*. Applicants submit that it would not require undue experimentation to perform *in vitro* experiments with a particular antisense oligonucleotide to determine the efficacy and effective dose of the proposed antisense usage in neoplastic cells. The use of antisense methods to inhibit the *in vitro* translation of genes is well known in the art. See, Marcus-Sakura (Anal. Biochem. 172: 289, 1988). Moreover, the *in vitro* use of cell lines for studies on potential antisense treatments for animal or human cancers are recognized in the art as a model that is predictive for subsequent animals or humans use. *In vitro* experiments provide relevant guidance for antisense therapy, which subsequently is predictable for *in vivo* or *ex vivo* use. According to the M.P.E.P. §608(p), the utility of a pharmaceutical can be shown by clinical or *in vivo* or *in vitro* evidence, or any combination. Applicants submit that it would not require undue experimentation to perform *in vitro* experiments to assess oligo efficacy for use in animals or humans.

In addition, many U.S. patents have issued for the use of antisense oligos, which would appear to be contradictory to the Examiner's position regarding the unpredictability of antisense oligos. (See, e.g., US Patent Nos. 5,620,963; 5,591,720; 5,591,623; 5,582,972; 5,563,255).

Applicant submits that one of skill in the art would accept *in vitro* antisense data as being reasonably predictive of utility in animals or humans. Therefore such data should be considered appropriate to support the credibility of the asserted utility. The guidance provided by the application provides sufficient teaching for therapeutic administration of the vectors of the invention containing antisense oligos, for use either *ex vivo* or *in vivo*. Applicants submit that the *in vitro* use of cell lines for studies on potential antisense treatments for animal or human cancers, for example, is an art recognized model and is predictive for use in animals or humans. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. §112 rejection.

Claims 1-2, 6, 13(c), 15-16, 18(e-f), and 19 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a cDNA molecule encoding the $TAF_{II}105$ polypeptide of SEQ ID NO:2 or SEQ ID NO:1 and a fragment thereof allegedly does not reasonably provide enablement for a "DNA molecule" encoding the $TAF_{II}105$ polypeptide of

SEQ ID NO:2, or a "DNA molecule" comprising SEQ ID NO:1 and a fragment thereof. Applicants respectfully traverse this rejection.

The Office indicates that the specification is enabling for a "cDNA". Applicants have amended the claims to recite "cDNA". Accordingly, this rejection may be properly withdrawn.

IV. REJECTION UNDER 35 U.S.C. §102

Claims 1-2, 13(c), and 15-16 stand rejected under 35 U.S.C. §102(b or e) as allegedly anticipated by Dikstein et al. (Cell, 87:137-146, 1996) and U.S. Patent No. 5,710,025. Applicants respectfully traverse this rejection..

Applicants respectfully submit that the cited references do not teach or suggest Applicants' claimed invention. For example, neither of the cited references teach or suggest a cDNA *consisting of* a sequence encoding a fragment of the $TAF_{II}105$ polypeptide wherein the fragment *has a dominant negative effect* on the normal biological activity of the $TAF_{II}105$ polypeptide. Applicants respectfully submit that a full length $TAF_{II}105$ polypeptide does not function in a dominant negative manner. Applicants respectfully submit that the "functional element" of the claim is not an intended use, but rather the functional activity of the claimed molecule. This functional activity in association with the structure recited in the claims clearly defines the metes and bounds of the invention and is patentable and non-obvious over the cited references. Thus, the cited references do not teach or suggest each and every element of Applicants' claimed invention. Accordingly, Applicants respectfully request withdrawal of the §102(b or e) rejection over Dikstein et al. and U.S. Patent No. 5,710,025.

V. REJECTION UNDER 35 U.S.C. §103

Claim 6 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Dikstein et al., and U.S. Patent No. 5,710,025, in view of U.S. Patent No. 4,889,806. Applicants respectfully traverse this rejection.

Claim 6 is a dependent claim that depends from claim 1. The Examiner is respectfully reminded that if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP §2143.03. Applicants submit that independent claim 1 is patentable and non-

obvious over Dikstein et al. and U.S. Patent No. 5,710,025 as discussed above. For example, neither of the cited references teach or suggest a cDNA consisting of a sequence encoding a fragment of the $TAF_{II}105$ polypeptide wherein the fragment has a dominant negative effect on the normal biological activity of the $TAF_{II}105$ polypeptide. Accordingly, Applicants respectfully request withdrawal.

Enclosed is a $55.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 7/25/03

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